REMARKS/ARGUMENTS

In response to the Office Action of September 24, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 36 and 41-43 have been amended. Claims 2-35 were cancelled in a previous response(filed on July 9, 2003). Claim 1 is withdrawn from consideration. It is understood that claim 1, drawn to a non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. Claims 1 and 36-43 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 21.

The description of the reference at page 4 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended for consistency of language in the figure descriptions.

The paragraph at page 21, beginning at line 7, has been amended to correct typographical errors.

The protocol at page 21, beginning at line 12, has been amended to correct typographical errors and to properly identify trademark names by capitalization.

The paragraph at page 22, beginning at line 2, has been amended to properly identify trademark names by capitalization.

The protocol at page 24, beginning at line 1, has been amended to correct typographical errors, punctuation errors, and to properly identify trademark names by capitalization.

The paragraph at page 24, beginning at line 15, has been amended to properly identify trademark names by capitalization.

The paragraph at page 27, beginning at line 6, has been amended to identify the name AMICON by capitalization. It is uncertain whether AMICON is a trademark or the name of a corporation since it has been cited as both.

The paragraph at page 27, beginning at line 17, has been amended for consistency of language.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 28, line 17 in order to provide explicit support for cerebrospinal fluid as recited in claim 38. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical

error within the same paragraph has also been amended (skill replaced skilled).

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (SEQ ID NO:1)and to clearly indicate that the claimed marker is isolated from its natural state by the methods described herein (see, for example, the instant specification at page 31, lines 9-12).

Claim 36 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:1) and congestive heart failure. Claim 36 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 36 find basis throughout the specification as originally filed, see, for example, page 17, lines 11-14, page 27, line 17 to page 28, line 2 and Figures 1 and 2.

Claim 41 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 18, lines 5-7. Claim 41 has been amended to correct an error in punctuation.

Claims 42 and 43 have been amended to provide proper

antecedent basis for the term "kit" in claim 41 (as amended herein).

Status of Prosecution Prior to Abandonment of Application

The last Office Action on the merits prior to the abandonment of the instant application was mailed on September 24, 2003 (paper #18). In the Office Action Summary (page 1), the Examiner indicated that the action was final by checking the box "This action is FINAL" box 2a). On page 2 of the action, the Examiner again indicates that the action is final in item #2. However, on page 3 of the action the Examiner presents new grounds of rejection and item #12 on page 11 indicates that these new grounds of rejection render the action non-final.

Thus, Applicants ask the Examiner for clarification on the status of the application prior to abandonment.

Applicants have responded herein as if the action mailed on September 24, 2003 is non-final based upon the introduction of new grounds for rejection.

Supplemental Response

The last Office Action on the merits prior to the abandonment of the instant application was mailed on September 24, 2003 (paper #18). This action was responsive to Applicants' response to the

first Office Action of April 7, 2003 filed on July 9, 2003. On October 2, 2003, Applicants filed a supplemental response to the Office Action of April 7, 2003. Since the Examiner mailed the last Office Action on the merits prior to abandonment of the application on September 24, 2003; the supplemental response of October 2, 2003 appears to not have been considered.

Thus, Applicants reiterate information from that supplemental response herein.

New Grounds of Rejection

Rejection under 35 USC 112, second paragraph

Claims 36-40, as presented on July 9, 2003, stand rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claims 36-40 are vague and indefinite because it is not clear as to what the biopolymer marker or analyte will entail. As cited the method is directed to a correlation of the unknown biopolymer with SEQ ID NO:1, however it is not clear as to what the final correlation will be. For example, does the biopolymer correlate to SEQ ID NO:1 as a 100% match, 90% match, etc. The Examiner indicates that appropriate correction is required.

New claim 36 clearly indicates that the mass spectrum profile of SEQ ID NO:1 is compared to the mass spectrum profiles of peptides obtained from the sample. Thus, mass spectrum profiles are correlated in the claimed method rather than biopolymers. The identification of a peptide by comparison of its mass spectrum profile with mass spectrum profiles of known peptides is a well known practice in the art.

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the rejection under 35 U.S.C. 112, second paragraph be withdrawn.

Double Patenting

Claims 36-40, as presented on July 9, 2003, stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 2-9 of US Patent 6,617,308 in view of Lewis et al. -Dale L. Oxender, Protein Structure, Folding, and Design 2, Alan R. Liss, Inc. New York, copyright 1987, page 417-427.

The Examiner alleges that although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to methods of comparing mass spectrum profiles of unknown peptides with the mass spectrum profile of a sequence identified as SEQ ID NO:1. Although the

instant application is directed to a 15 amino acid structure differing in one terminal amino acid (Ser) the elimination of a terminal amino acid is taught not always critical for activity. On page 420, 4th paragraph, Lewis et al. teach that the N-terminal 6 amino acids were not required for activity in IL-3 molecules. Further Lewis et al. teach that smaller proteins and/or peptides can be purified more readily than the larger ones. See page 420, 1st paragraph. The Examiner concludes that, therefore, the instant invention is encompassed within US Patent 6,617,308.

Applicants respectfully disagree with the Examiner's determination of double patenting between claims 36-40 of the instant application and claims 2-9 of US Patent 6,617,308.

SEQ ID NO:1 of the instant application is a fragment of complement C3f protein consisting of 15 amino acid residues, SKITHRIHWESASLL. SEQ ID NO:1 of US Patent 6,617,308 is a fragment of complement C3f protein consisting of 16 amino acid residues, SSKITHRIHWESASLL. Although the sequences differ only in one terminal amino acid residue (Ser); both sets of claims (36-40 of the instant application and 2-9 of US Patent 6,617,308) recite the language "consisting of". Since the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claims now encompasses only this specific peptide (SEQ ID NO:1, 15

amino acid residues in length), thus excluding SEQ ID NO:1 of US Patent 6,617,308 from the scope of the claims (claims 36-40 of the instant application).

The Examiner cites an article Lewis et al. -Dale L. Oxender, Protein Structure, Folding, and Design 2, Alan R. Liss, Inc. New York, copyright 1987, page 417-427 which is allegedly relevant to the instant invention.

Clark-Lewis et al. discover from their experimentation that the synthetic form of both the mature IL-3 molecule (amino acid residues 1-140)and the shortened form (amino acid residues 7-140) have equivalent activity, indicating that N-terminal 6 amino acids are not required for activity. The Examiner appears to believe that the teaching of Clark-Lewis regarding the biological activity of IL-3 is relevant to the instant invention.

Applicants respectfully disagree with the Examiner's reliance on the article of Clark-Lewis et al.

While Clark-Lewis et al. do teach that the N-terminal 6 amino acid residues of IL-3 are not required for activity, they also teach in the next paragraph that a peptide corresponding to amino acid residues 1-79 of IL-3 has detectable activity (page 420, 4th paragraph under "Interleukin-3 Structure-Function Studies"). Thus, the teachings of Clark-Lewis et al. do not definitively establish the activity of the N-terminal 6 amino acids of IL-3.

Furthermore, both the method of the instant invention and the method of US Patent 6,617,308 involve the comparison of mass spectrum profiles in order to identify potential disease markers from patient samples. Knowledge regarding the biological activity of the potential disease markers is not necessary to practice the claimed invention or the invention of US Patent 6,617,308. Thus, the results of the structure-function studies of Clark-Lewis et al. are irrelevant to the instant invention.

Additionally, the research of Clark-Lewis et al. focuses on interleukin-3, a protein which is distinct from that protein which is focused on by the instant invention, complement C3. Interleukin-3 is a known cytokine secreted by lymphocytes and acts upon other lymphocytes. Complement C3 is a known component of the complement system of serum proteins. Thus, a direct correlation can not be made between the teachings of Clark-Lewis et al. and the teachings of the instant invention and/or US Patent 6,617,308.

In light of all of the above remarks, Applicants respectfully contend that a biologist of ordinary skill in the art, having the Clark-Lewis et al. reference and US Patent 6,617,308 in front of him/her would not have the information and motivation necessary to arrive at Applicants' invention.

Thus, it is respectfully submitted that the combination of the Clark-Lewis et al. reference and US Patent 6,617,308 fails to

reasonably teach or suggest to one of ordinary skill in the art the elements of Applicants' method as specifically set forth in claims 36-40 as presented herein.

Accordingly, Applicants have clarified that the pending claims of the instant application are, in fact, patentably distinct from the claims of US Patent 6,617,308 and thus respectfully request that this rejection under the judicially created doctrine of double patenting now be withdrawn.

Maintained Rejections

Rejection under 35 USC 112, first paragraph

Claims 36-43 (previously 3-9, 18-28 and 33-35), as presented on July 9, 2003, remain rejected under 35 USC 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons made of record in the previous Office Action mailed on April 7, 2003.

The Examiner has responded to previous arguments (July 9, 2003)by indicating that Applicants argue that they are currently in the process of preparing a Declaration under 37 CFR 1.132 in order to provide evidence of the absence of the 1793 dalton

biopolymer marker (SEQ ID NO:1) in normal human sera. The Examiner asserts that until receipt of the Declaration and review of the evidence the rejection is maintained.

Applicants submitted a Declaration under 37 CFR 1.132 with the "Supplemental Response to the Office Action of April 7, 2003" which was filed on October 2, 2003. As previously indicated in the instant response, this supplemental response was not considered since it was received in the Office after the mailing date of the last action prior to abandonment of the application. Thus, Applicants submit a copy of this Declaration herewith.

The Examiner asserts that claims 36-43 are broadly drawn to methods of determining the presence or absence of congestive heart failure by analyzing a biological sample obtained from a patient to identify a biopolymer marker sequence whose mass spectrum profile displays the characteristic profile of a sequence identified as SEQ ID NO:1. The specification asserts that the said target sequence was found in congestive heart failure. However, the Examiner asserts that the obtained results set forth in the specification for the example in figure 1 are not clearly indicative of congestive heart failure because no control sample analysis is presented by way of example.

Applicants respectfully disagree with the Examiner's determination that the claimed subject is not enabled and in

response to the Examiner's assertion regarding control samples, Applicants herein provide a Declaration (including a figure) under 37 CFR 1.132. The figure attached to the Declaration provides both a mass spectrum profile of normal human sera and a mass spectrum profile of sera obtained from patients having a history of congestive heart failure. The profiles are shown in a side-by-side comparison. This profile comparison clearly evidences the absence of the 1793 dalton marker in normal human sera and thus establishes the ability of the 1793 dalton marker to distinguish normal patients from patients having a history of congestive heart failure. This figure does not represent results obtained from additional experimentation. The mass spectrum profiles shown were reproduced from data obtained in the original experiments performed at the time of the invention.

Thus, contrary to the Examiner's assertion, the experiments described in the instant specification were carried out using control samples.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:1 is diagnostic for congestive heart failure, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:1 is linked

to congestive heart failure.

According to the web site, dictionary.com, the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). The instant specification fully supports a connection and/or an association of the claimed peptide with congestive heart failure. The instant specification states at page 17, lines 11-14 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:1, a peptide which the instant specification identifies as related to congestive heart failure. Claim 1, as amended herein, does not recite that the claimed

isolated peptide is diagnostic for congestive heart failure, nor does it recite that the claimed isolated peptide is related to congestive heart failure, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide.

A table comprising data collected from 20 patients having a history of congestive heart failure (CHF) is shown in Figure 1. The claimed biopolymer marker (SEQ ID NO:1; a fragment of complement protein C3f weighing 1793 daltons) was found to be present in the sera of all 20 patients. A mass spectrum profile from one of these patients is shown in Figure 2. The Declaration attached hereto provides evidence that the claimed biopolymer marker (SEQ ID NO:1; a fragment of complement protein C3f weighing 1793 daltons) was not found in sera obtained from individuals determined to be normal with regard to congestive heart failure.

Thus, Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:1) is linked and/or associated with congestive heart failure.

The Examiner asserts that it is not clear how the same

biopolymer marker will be utilized to distinguish any and all disease states. In other words how will one identify any disease state by detecting and comparing the mass spectral profiling of SEQ ID NO:1 with various peptides in a sample.

Applicants respectfully assert that it is clear that the data obtained by the experiments disclosed in the instant specification was obtained by using techniques of mass spectrometry; see, for example, page 20, lines 2-6 and Figure 2). Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. For example, one of ordinary skill in the art would compare the mass spectral profile of SEQ ID NO:1, as disclosed in the instant specification as Figure 2, with mass spectral profiles of peptides obtained from a patient sample in order to ascertain if SEQ ID NO:1 is present in the sample.

Thus, contrary to the Examiner's assertion, it is clear how one will identify any disease state by detecting and comparing the mass spectral profile of SEQ ID NO:1 with mass spectral profiles of various peptides in a sample.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass

spectrometric protocols presented in the instant specification in order to use the claimed invention.

The specification, as originally filed, provides a precise protocol on how to analyze the data obtained from the disclosed method. Page 12, lines 2-12, of the instant specification discloses a general outline of how to carry out the disclosed methods. Page 20, lines 2-4 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 2). This conference took place in 2000, thus coinciding with the time that the instant

inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification. Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference

by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants

respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

The data presented in Figures 1 and 2, derived from the working examples, discloses that the claimed marker (SEQ ID NO:1)is found in the sera of patients having a history of congestive heart failure, thus it can be reasonably predicted that such marker is linked to congestive heart failure.

Thus, Applicants contend that a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker (SEQ ID NO:1) and congestive heart failure.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known

in the prior art without undue experimentation.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including, for example: Applicants have not provided any disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said sequence.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. The pending claims do not recite any methods which definitively assess the incidence of congestive heart failure or any other disease state. Furthermore, the pending claims do not recite any disease state other than congestive heart failure, nor do the pending claims recite methods of regulating the sequence or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence for enablement of the pending claims.

The Examiner asserts that Applicants have not set forth any supporting evidence that suggests that any of the sequences (SEQ ID NO:1) are unique molecular markers for congestive heart failure

and all other possible disease states.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Applicants assert that SEQ ID NO:1 is linked to congestive heart failure, however, do not claim that SEQ ID NO:1 is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed SEQ ID NO:1, a fragment of complement protein C3f, is related to congestive heart failure, it does recognize that inflammation is related to congestive heart failure (see attached abstract of Gottdiener et al. Journal of the American College of Cardiology 35(6):1628-1637 2000; reference 3). When one of skill in the art observes the presence of the claimed marker (SEQ ID NO:1) in sera obtained from patients having a history of congestive heart failure and the absence of the claimed marker (SEQ ID NO:1) in sera obtained from healthy patients; one of skill in the art will connect this marker with potential diagnostics and/or therapeutics for congestive heart failure.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed peptide(SEQ

ID NO:1) and congestive heart failure and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of congestive heart failure, the requirement of "how to use" under 35 USC 112, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:1) and congestive heart failure to be reasonable.

At page 27, of the instant specification as originally filed, SEQ ID NO:1 is identified as a fragment of the complement protein C3f. Elevated levels of complement proteins have been reported in patients with advanced heart failure (see attached abstract of Kosar et al. Angiology 50(5):403-408 1999; reference 4). Additionally, it has been found that both the alternative and classical pathways of complement are activated during VAD circulation (see attached abstract of Chen et al. Journal of Investigative Medicine 47(9):502-506 1999; reference 5). A ventricular assist device, i.e. VAD, is used as therapy in heart failure patients (see attached abstract of Argenziano et al. Japanese Circulation Journal 61(11):887-892 1997; reference 6). One of skill in the art, considering the known involvement of inflammation and complement activation in heart failure, upon observation of the presence of the claimed marker (SEQ ID NO:1) in

sera obtained from patients having a history of congestive heart failure and the absence of the claimed marker (SEQ ID NO:1) in sera obtained from healthy patients, would find it reasonable to believe that this marker is related to congestive heart failure.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:1, inflammation, complement activation and congestive heart failure and thus would also find the suggestion of SEQ ID NO:1 as a marker for congestive heart failure entirely reasonable.

The Examiner cites two articles; Tascilar *et al.* (see attached abstract, Annals of Oncology 10, Supplement 4:S107-S110 1999; reference 7) and Tockman *et al.* (see attached abstract, Cancer Research 52:2711s-2718s 1992; reference 8) which are allegedly relevant to the instant invention.

According to the Examiner, Tascilar *et al.* is an article published in an oncogenic journal reporting on diagnostic methods in the realm of disease states. The Examiner appears to have drawn a direct parallel between the diagnostic methods reported by Tascilar *et al.* and the diagnostic methods described in the instant invention. The Examiner then cites two fragmented quotations from Tascilar *et al.* "...these tests should be interpreted with caution..." and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently".

The Examiner appears to be commenting on the predictability of molecular-based assays.

Applicants respectfully disagree with the Examiner's reliance on the article by Tascilar et al.

Applicants assert that the claimed peptide (SEQ ID NO:1) is linked to congestive heart failure; a statement which is enabled by the description of methods as set forth in the specification and by data presented in Figures 1 and 2. Thus, Applicants respectfully submit that the claimed method involves a simple observation of the levels of expression of SEQ ID NO:1 (as shown in Figures 1 and 2) and does not require any other evaluation of genetic changes in the organism in which the sequence is observed.

Furthermore, the study of Tascilar et al. is concerned with the evaluation of samples for genetic mutations (K-ras and p53 mutations) for early detection of pancreatic cancer (see attached abstract of Tascilar et al. Annals of Oncology 10, Supplement 4:S107-S110 1999; reference 7). It appears that Tascilar et al. suggest that protein markers may be useful for early detection of pancreatic cancer; however there does not seem to be any other reference to protein markers, thus the study of the instant inventors (drawn to protein markers and not to genetic markers) is not analogous to the study of Tascilar et al.

Accordingly, Applicants respectfully submit that the Tascilar

et al. article is not relevant to the instant invention.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992; reference 8) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. According to the Examiner, Tockman *et al* reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life experience within a population with a disease or disorder are highly speculative and unpredictable.

Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects

monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants also respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for congestive heart failure.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:1) and congestive heart failure.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05)

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the

considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

In conclusion, Applicants claim that the presence of SEQ ID NO:1 in sera obtained from congestive heart failure patients and the absence of SEQ ID NO:1 in the sera of patients determined to be healthy with regard to congestive heart failure evidences a link between the claimed peptide (SEQ ID NO:1) and congestive heart failure; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:1) and congestive heart failure and would further recognize how to use the claimed peptide (SEQ ID NO:1) as a marker for congestive heart failure. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

Rejection under 35 USC 101

Claims 36-43 (previously 3-9, 18-28 and 33-35), as presented on July 9, 2003, remain rejected under 35 USC 101 because the claimed invention allegedly is not supported by either a specific, substantial, credible or asserted utility or a well-established utility.

This rejection is maintained for reasons made of record in the previous Office Action mailed on April 7, 2003.

The Examiner has responded to previous arguments (July 9, 2003)by asserting that Applicant contends that SEQ ID NO:1 is detectable only in congestive heart failure but undetectable in other diseases related to syndrome X. The Examiner asserts that this argument was not found persuasive because SEQ ID NO:1 is encompassed by US 6,617,308 wherein the sequence is used as a marker for not only congestive heart failure but myocardial infarction and Type II diabetes. The Examiner asserts that it is not clear how the same marker is indicative of all the previously mentioned disorders and thus, the rejection is maintained.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility.

The Examiner continues to maintain that Applicant has stated

that SEQ ID NO:1 is detectable only in congestive heart failure but undetectable in other disease states related to syndrome X.

Applicants respectfully assert that this statement made by the Examiner is incorrect.

Applicants contend that SEQ ID NO:1 is a positive indicator of congestive heart failure; however, no where in the specification or in the previous response (filed on July 9, 2003) do Applicants contend that SEQ ID NO:1 is only detectable in congestive heart failure nor do Applicants contend anywhere in the specification or in the previous response that SEQ ID NO:1 is undetectable in other disease states related to SEQ ID NO:1.

The Examiner asserts that because SEQ ID NO:1 is encompassed by US 6,617,308 wherein the sequence is used as a marker for not only congestive heart failure but myocardial infarction and Type II diabetes, it is not clear how the same marker is indicative of all the previously mentioned disorders.

Apparently, the Examiner believes that if a marker is found to be indicative of a disease state it is simultaneously excluded from being indicative of any other disease state.

It is well known that complement components have been implicated in the pathogenesis of several disease conditions, see the instant specification at page 14, lines 12-13. By carrying out the claimed methods, Applicants have identified a mass spectral

profile of SEQ ID NO:1 (profile shown in Figure 2). This mass spectral profile is meant to function as a reference for comparison of mass spectral profiles obtained from unknown samples. If the mass spectral profile of SEQ ID NO:1 is identified in a sample, then that sample can be linked to congestive heart failure. This protocol can be applied to any disease state (see the instant specification at page 12, lines 13-17 and page 26, lines 20-22).

Thus, contrary to the Examiner's assertion, it is clear how a marker is determined to be indicative of a disease state.

Furthermore, US Patent 6,617,308 and the instant application both disclose fragments of complement protein C3f which were determined to be indicative of disease. SEQ ID NO:1 of the instant application is a fragment of complement C3f protein consisting of 15 amino acid residues, SKITHRIHWESASLL. SEQ ID NO:1 of US Patent 6,617,308 is a fragment of complement C3f protein consisting of 16 amino acid residues, SSKITHRIHWESASLL. Although the sequences differ only in one terminal amino acid residue (Ser); the claims (36-40) of the instant application recite the language "consisting of". Since the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claims now encompasses only this specific peptide (SEQ ID NO:1, 15 amino acid residues in length), thus excluding SEQ ID NO:1 of US Patent 6,617,308 from the

scope of the claims (claims 36-40 of the instant application).

Accordingly, the marker disclosed in US Patent 6,617,308 is not identical to the marker disclosed in the instant invention, and thus can not be considered to have any relevance to the utility of the instant invention.

The Examiner sites three patent references, US 5,849,297; US 6,221,657 and US 6,268,485, which allegedly provide information which is contradictory to the instant invention. The Examiner asserts that these patents disclose the same sequence as SEQ ID NO:1 of the instant invention and further that this sequence has utility in myocardial infarction, ischemia, frostbite, burns, glomerulonephritis, hemolytic anemia, myasthenia gravis and Type II diabetes induced arthritis.

These patents disclose the entire peptide sequence of complement protein C3 and do not disclose the specific SEQ ID NO:1 of the instant invention. The claims, as currently pending, recite the phrase "consisting of" , which is closed language and excludes any element, step, or ingredient not specified in the claims (see MPEP 2111.03). The claims, as currently pending, are limited to the specific SEQ ID NO:1; thus, excluding the proteins disclosed in the patents (US 5,849,297; US 6,221,657 and US 6,268,485).

Furthermore, these patents disclose methods (and proteins made by the methods) for modifying human C3 complement proteins such

that the complement proteins are capable of forming stable C3 convertases. These modified complement C3 convertases function to deplete the levels of complement pathway proteins and are thus useful as therapeutic agents in certain clinical situations, such as myocardial infarction, ischemia, frostbite, burns, glomerulonephritis, hemolytic anemia, myasthenia gravis and Type II diabetes induced arthritis. These patents do not teach modified complement C3 convertases which are useful as diagnostics. The list of clinical situations cited in the patent are not, contrary to the Examiner's assertion, a list of diseases for which the modified C3 complement protein is indicative of, but a list of conditions that may be treatable with the modified C3 complement proteins. Therefore, the teachings of the patents cited by the Examiner (US 5,849,297; US 6,221,657 and US 6,268,485) are not analogous to, but unrelated to the teachings of the instant invention.

Accordingly, Applicants respectfully submit that the patent references (US 5,849,297; US 6,221,657 and US 6,268,485) are not relevant to the instant invention.

Applicants assert that SEQ ID NO:1 is useful for diagnosis and treatment of congestive heart failure since it was found to evidence a link to congestive heart failure (an "asserted" utility). The asserted utility is supported by the data derived from the working examples which show that the claimed marker is

found in the sera of patients having a history of congestive heart failure (see Figures 1 and 2).

The Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the claimed marker (SEQ ID NO:1).

Additionally, it has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

Thus, Applicants respectfully assert that it is improper for the Examiner to assert that SEQ ID NO:1 has no utility as a marker for congestive heart failure in light of the data shown in Figures 1 and 2.

Furthermore, Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-10; page 17, lines 11-14; page 27, line 17 to page 28, line 2; and Figures 1 and 2).

In the instant invention, the claimed peptide (SEQ ID NO:1) is not shown to evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, congestive heart failure, thus the invention has a specific utility as a marker for congestive heart failure whether or not it can also function as a marker for another disease(s).

Additionally, if an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

Advances in diagnosis and treatment of congestive heart failure are highly desirable considering that congestive heart failure is a significant source of morbidity and mortality in the elderly population; diagnostics are especially relevant since the elderly population is increasing. Thus, advances in diagnosis and treatment of congestive heart failure would greatly benefit a population which is susceptible to the adverse effects of congestive heart failure.

The claimed marker (SEQ ID NO:1) represents an advance in congestive heart failure research; a "real-world" use benefitting the public (elderly population susceptible to congestive heart failure), which satisfies the precedent set in *Nelson*. Thus, the claimed marker (SEQ ID NO:1) additionally has a substantial utility

based upon a "real-world" use.

The Examiner further asserts that there is no disclosure or working examples that demonstrate the specifically asserted utility and evidences a substantial utility was well-established at the time of filing. Further, the Examiner alleges that it is not clear how the same biopolymer marker will be used to distinguish various unrelated disease states.

The claims, as currently pending, do not recite an ability to distinguish between disease states; but rather that the claimed biopolymer marker (SEQ ID NO:1) evidences a link to congestive heart failure. The claimed biopolymer marker (SEQ ID NO:1) was identified in sera obtained from patients having a history of congestive heart failure and was not identified in the sera obtained from individuals determined to be normal with regard to congestive heart failure. The presence of the marker in the disease state, congestive heart failure, and the absence of the marker in the normal physiological state indicates that this marker may be linked to congestive heart failure, thus supporting the claims as currently pending.

In the search for specific biomarkers, proteins found to be differentially expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 2). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the instant invention, peptides are selected as potential markers by their presence in a disease state versus a normal state. Such selection methods, based upon differential expression of peptides, are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice in proteomics to select potential disease markers by their differential expression between a disease and a non-disease state.

Accordingly, when one of skill in the art observes the claimed peptide identified in sera obtained from patients having a history

of congestive heart failure and observes the absence of the claimed peptide in a normal physiological state; one of skill in the art would connect the peptide with potential diagnostics and/or therapeutics for congestive heart failure and would immediately appreciate why Applicants regard the claimed marker (SEQ ID NO:1) as useful, indicating that the utility of the claimed marker is well-established.

Inflammation is known to be related to congestive heart failure (see attached abstract of Gottdiener et al. Journal of the American College of Cardiology 35(6):1628-1637 2000; reference 3). Elevated levels of complement proteins have been reported in patients with advanced heart failure (see attached abstract of Kosar et al. Angiology 50(5):403-408 1999; reference 4). Additionally, it has been found that both the alternative and classical pathways of complement are activated during VAD circulation (see attached abstract of Chen et al. Journal of Investigative Medicine 47(9):502-506 1999; reference 5). A ventricular assist device, i.e. VAD, is used as therapy in heart failure patients (see attached abstract of Argenziano et al. Japanese Circulation Journal 61(11):887-892 1997; reference 6).

At page 27 of the instant specification as originally filed, SEQ ID NO:1 is identified as a fragment of the complement protein C3f. One of skill in the art, considering the known involvement

of inflammation and complement activation in heart failure, upon observation of the presence of the claimed marker (SEQ ID NO:1) in sera obtained from patients having a history of congestive heart failure and the absence of the claimed marker (SEQ ID NO:1) in sera obtained from healthy patients, would find it reasonable to believe that this marker is related to congestive heart failure.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:1, inflammation, complement activation and congestive heart failure and thus would also find the suggestion of SEQ ID NO:1 as a marker for congestive heart failure entirely reasonable.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph (based on 35 USC 101)

Claims 36-43 (previously 3-9, 18-28 and 33-35), as presented on July 9, 2003, remain rejected under 35 USC 112, first paragraph. Specifically the Examiner asserts that since the claimed invention is not supported by a specific, substantial or credible asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

It has been established by prior arguments in the instant Response that the claimed invention has both a specific and a well established utility. Therefore, Applicants respectfully request that the Examiner now withdraw the rejection under 35 USC 112, first paragraph which was based upon the rejection under 35 USC 101.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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Examiner copy
reference #1

6 entries found for *linked.*

link[1] ngk)
n.

One of the rings or loops forming a chain.

A unit in a connected series of units: *links of sausage; one link in a molecular chain.*

A unit in a transportation or communications system.

A connecting element; a tie or bond: *grandparents, our link with the past.*

An association; a relationship: *The Alumnae Association is my link to the school's present administration.*

A causal, parallel, or reciprocal relationship; a correlation: *Researchers have detected a link between smoking and heart disease.*

A cuff link.

Abbr. **li** A unit of length used in surveying, equal to 0.01 chain, 7.92 inches, or about 20.12 centimeters.

A rod or lever transmitting motion in a machine.

Computer Science. A segment of text or a graphical item that serves as a cross-reference between parts of a hypertext document or between files or hypertext documents. Also called **hotlink, hyperlink**.

* as accessed from dictionary.com